PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	See form PCT/ISA/210
Applicant's or agent's file reference RS 343 WO - AB/CG	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FR2005/000713	25.03.2005	29.03.2004

International Patent Classification (IPC) or both national classification and IPC
A61 K31/5415, A61 K45/06, A61 P27/16

Applicant
SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2005/000713

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2005/000713

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-23	YES
	Claims	24-29	NO
Inventive step (IS)	Claims	-	YES
	Claims	1-29	NO
Industrial applicability (IA)	Claims	1-29	YES
	Claims		NO

2. Citations and explanations:

i. Reference is made to the following documents:

D1: WO 01/32654 A (AUVIN SERGE; CHABRIER DE LASSAUNIERE PIERRE (FR); SOD CONSEILS RECH A) 10 May 2001 (2001-05-10)

D2: WO 02/40016 A (PIGNOL BERNADETTE; AUVIN SERGE (FR); CHABRIER DE LASSAUNIERE PIERRE) 23 May 2002 (2002-05-23)

ii. PCT Article 33(2)

The present application fails to comply with the requirements of PCT Article 33(1) since the subject matter of claims 24-29 does not meet the requirement of novelty defined in PCT Article 33(2).

(a) The scope of the protection sought for claims 24-29, as they are formulated, is considered to be a "first therapeutic use". Claims formulated in this way are only permitted if no prior therapeutic use exists. Therefore, any document which discloses the use of a heterocyclic derivative of formula (I) in combination with another substance with therapeutic activity, in therapy, is relevant with respect to the novelty of claims 24-29.

(b) In addition, in a claim which relates to a preparation of a known active substance, with a defined structure, comprising at least one substance with therapeutic activity, in which the feature "and at least one substance with therapeutic activity" means that another active ingredient is added to the active substance, the addition to the mixture of a substance with undetermined therapeutic activity cannot, given the unlimited number of substances which come into consideration, be considered to be a concrete supplement, which is distinctive in nature, given to this first active substance, as long as this feature necessary for the novelty of the invention to be recognized is not a concrete feature which allows a person skilled in the art to observe what must be added to this active substance.

(c) Document D1 discloses phenothiazine derivatives which correspond to the compounds of the present application (page 1, lines 1-10; page 2, lines 5-6; page 3, line 17 - page 4, line 9; page 7, lines 1-4 and 23; page 8, lines 5-8 and 15-21; page 11, line 3 - page 12, line 16; page 19, line 21 - page 27, line 3; page 27, line 11 - page 28, line 18; claims 12-18 and 23) and also pharmaceutical compositions comprising, as active ingredient, at least one of these compounds (page 18, line 17 - page 19, line 16; claim 11). This implies that a combination of several compounds of formula (I) is also disclosed in D1. Consequently, in view of points **ii(a)-(b)**, the subject matter of claims 24-29 is not novel with respect to D1.

iii. PCT Article 33(3)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

(a) The problem that the present invention is intended to solve is the provision of an alternative medicament for the prevention and/or treatment of hearing loss.

The solution as proposed is the use of a phenothiazine derivative having a calpain-inhibiting activity and a reactive oxygen species-trapping activity (page 1, lines 1-6).

(b) The present application fails to comply with the requirements of PCT Article 33(1) since the subject matter of claims 1-29, as far as it is novel, does not involve an inventive step as defined in PCT Article 33(3).

(c) Document D2, which is considered to be the closest prior art, describes the use of a combination of calpain inhibitors and reactive oxygen species-trapping agents for the treatment of pathologies in which these enzymes and/or these free-radical species are involved, such as hearing loss (page 1, lines 1-27; page 2, lines 21-27; page 4, lines 1-12; page 12, lines 14-25; claims 1, 2, 9-12, 20 and 23). Preferably, the reactive oxygen species-trapping agents can be phenothiazines (page 6, line 11 - page 7, line 12; page 11, line 28 - page 12, line 2) and the calpain inhibitors can be amino acid derivatives, such as, for example, Z-Leu-Leu-H or Z-Leu-Phe-H (page 12, lines 3-13; example 2).

The subject matter of claims 1-29, as far as it is novel, differs therefrom in that a single compound, combining the calpain-inhibiting activity and the reactive oxygen species-trapping activity, is used for the same therapeutic purpose.

The problem that the present invention is intended

to solve can thus be considered to be that of the provision of an alternative medicament having a calpain-inhibiting activity and a reactive oxygen species-trapping activity, for the prevention and/or treatment of hearing loss.

The solution, as proposed in independent claim 1 of the present application, is not considered to be inventive (PCT Article 33(3)) for the following reasons:

From document D1, it is known that the compounds of the present invention have a calpain-inhibiting activity and/or a reactive oxygen species-trapping activity and that they can be used for all pathologies in which ROSs and calpains are involved (see also point **ii**).

Consequently, it is considered that a person skilled in the art would inevitably have been led to use these compounds for the treatment of hearing loss, expecting a positive result therefrom.

In the absence of convincing arguments and/or of additional data demonstrating an unexpected and/or surprising effect related to the use of the compounds of the present application compared with that of the compounds of D2, the solution proposed in independent claim 1 cannot be considered, at present, to involve an inventive step (PCT Article 33(3)).

(d) Dependent claims 2-23 and 25-29 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (PCT Article 33(3)).

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2005/000713

Box No. VI Certain documents cited

1. Certain published documents (Rule 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date (day/*month*/*year*)	Filing date (day/*month*/*year*)	Priority date (valid claim) (day/month/*year*)

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/*month*/*year*)	Date of written disclosure referring to non-written disclosure (day/month/*year*)

See form 210

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2005/000713

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The terms "at least one other substance with pharmaceutical activity", "at least one other substance with pharmaceutical activity capable of preventing and/or treating hearing loss or else of preventing and/or treating any hearing loss-associated pathologies" and "at least one substance with therapeutic activity", used in claims 21-22 and 24-29, are vague and equivocal and cast doubt on the meaning of the technical features to which they refer. The subject matter of said claims is thus not clearly defined (PCT Article 6).

In addition, claim 22 fails to comply with the requirements of PCT Article 6 in so far as the subject matter for which protection is sought has not been clearly defined. Claim 22 attempts to define said subject matter in terms of the result to be achieved, in particular "at least one other substance with pharmaceutical activity capable of preventing and/or treating hearing loss or else of preventing and/or treating any hearing loss-related pathologies", yet this merely amounts to stating the basic problem the invention is intended to solve, without providing the technical features required to achieve this result.